SYNTHESIS AND FIBRINOLYTIC ACTIVITY OF β-ARYLALIPHATIC ACIDS. QUANTITATIVE RELATIONSHIPS BETWEEN STRUCTURE AND BIOLOGICAL ACTIVITY

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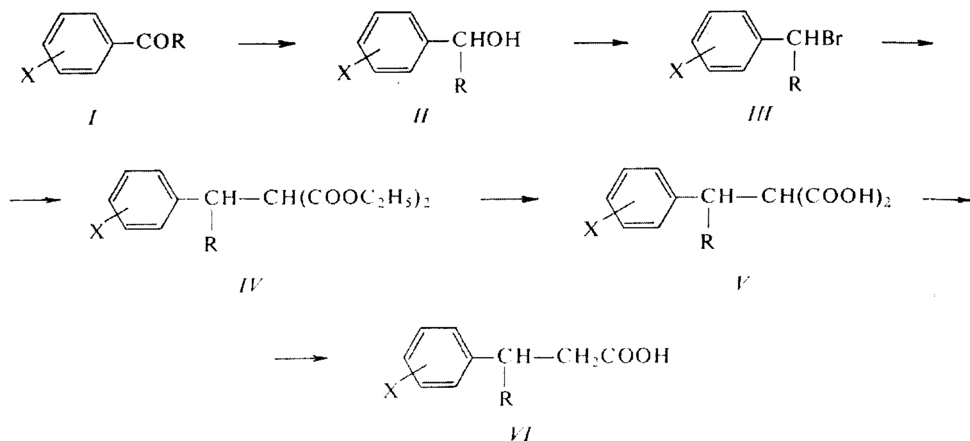
A series of β-arylaliphatic acids *VI* was prepared from starting alkylaryl ketones *I via* 1-(aryl)-alkanols *II* and bromides *III*. Their condensation with ethyl malonate led to 1-(aryl)alkyl malonates *IV* which were hydrolyzed and decarboxylated to acids *VI*. These acids were tested as activators of fibrinolysis and their effect on the inhibition of denaturation of serum albumin was examined. Using the Hansch method of correlation analysis the fibrinolytic activity was found to be affected first of all by the lipophilicity of these acids and to a smaller extent by the steric or induction effect of the alkyls in β-position with respect to carboxyl. From the similarity of the relationships of the two activities and the physico-chemical parameters one can infer that the binding of protein plays an important role in the mechanism of activation of fibrinolysis.

It was found that an important property of most non-steroid antiinflammatory agents of acid nature is the activation of fibrinolysis[1-3]. The fact that so far no synthetic clinically useful fibrinolytic exists stimulates the study of these antiinflammatory agents from the point of view of their fibrinolytic activity. Hence we examined the effect on activation of fibrinolysis of a series of β-arylaliphatic acids prepared in connection with the investigation of antiinflammatory agents containing carboxyl in their molecule[4,5].

To synthesize the β-arylaliphatic acids we used the method of Asano and coworkers[6] starting from alkyl aryl ketones *I*. The ketones were reduced with sodium borohydride in aqueous methanol to 1-(aryl)alkanols *II* which were isolated by distillation and their purity checked by gas chromatography in reference to the starting ketone. Alcohols *II* were converted to the corresponding bromo derivatives *III* in a reaction of phosphorus tribromide in ether in the presence of pyridine. The compounds were isolated by distillation and evaluated by gas chromatography. In a further step 1--(aryl)alkylmalonates *IV* were prepared by alkylation of ethyl malonate with bromides *III* in the presence of sodium ethylate. After distillation, the substituted malonates *IV* were identified by elementary analysis, compounds *IVj*, *IVk* and *IVt* were identified only after saponification to malonic acids. After saponification in aqueous–ethanolic potassium hydroxide, the malonic acids formed (*V*) were decarboxylated without further purification by heating to 200°C to yield the final β-arylaliphatic acids *VI* (Scheme 1). In view of the complicated reduction of *p*-methoxyacetophenone with so-



R = CH_3, X: *a*) H; *b*) 4-OCH_3; *c*) 4-CH_3; *d*) 4-Cl; *e*) 3-CF_3; *f*) 4-Br; *g*) 4-C_2H_5; *h*) 3-Br; *i*) 4-iso-C_3H_7; *j*) 4-C_6H_5; *k*) 4-iso-C_4H_9; *l*) 4-OH;
R = C_2H_5, X: *m*) H; *n*) 4-CH_3; *o*) 4-Cl; *p*) 4-iso-C_4H_9;
R = iso-C_3H_7, X: *r*) H; *s*) 4-CH_3; *t*) 4-iso-C_4H_9;
R = n-C_3H_7, X: *u*) H; *v*) 4-CH_3; *w*) 4-Cl

SCHEME 1

dium borohydride, acid *IVb* was prepared by a Reformatsky synthesis[7]; the *para*-hydroxy derivative *VII* was obtained by subsequent demethylation with hydrobromic acid.

Acids *VI* were identified by elementary analysis, IR and ^{1}H-NMR spectra. The IR spectra shown contain the maxima characteristic for carboxyl (about 1710 cm^{-1}) and bands corresponding to substitution at the aromatic ring, in the region of about 830 cm^{-1} for *para* and at about 700 cm^{-1} for *meta* substitution. Of the ^{1}H-NMR spectra, Table I summarizes the signals of protons of the basic structure of β-arylaliphatic acids. In acids *VIr*, *VIs* the protons of both methyl groups in the isopropyl are separated into two doublets by prevention of their free rotation. In acid *VIt* they merge into a single doublet which is apparently due to the mutual interference of the protons of all the four methyls in the *p*-isobutyl and the β-isopropyl residue. The proton signals in both methylene groups of n-propyl merge into an inseparable multiplet.

The *pK* values of acids *VI* determined conductometrically[8] in water were correlated with physico-chemical parameters of the substituents at the aromatic ring and of alkyls in the β-position with respect to carboxyl. Thus the regression equations (*1*) and (*2*) were derived:

	n	*s*	*r*	*F*	
$pK = -0.2575\sigma - 0.3091E_S + 4.6539$	22	0·0192	0·9771	200·4,	(*1*)
$pK = -0.2533\sigma - 0.7766\sigma^* + 4.6464$	22	0·0233	0·9661	132·9,	(*2*)

where σ are Hammett's constants of aromatic substituents, σ^* are Taft's constants and E_S are the steric parameters of the alkyls at the C_β atom; n is the number of substances, s is the standard deviation, r the correlation coefficients and F the Fischer–Snedecor criterion. In view of the similar values of the statistical criteria in both equations which are due to the relationship between parameters E_S and the σ^* constants in the given series of substituents R ($E_S = 2{\cdot}5425\sigma^* + 0{\cdot}0324$ $n = 4$, $s = 0{\cdot}1313$, $r = 0{\cdot}8800$, $F = 6{\cdot}87$) one cannot decide unequivocally about the character of the effect of β-alkyls on the dissociation of acids *VI*. The pK values used in biological correlations were computed from equation (*1*) and are shown together with the experimental data in Table I.

To evaluate quantitatively the fibrinolytic activity the "hanging clot" method according to von Kaulla was used[20]. The experimental results obtained by determining the fibrinolytic activity of a great number of different types of organic acids led von Kaulla to the conclusion that the compounds are characterized by a hydrotropic activity. This assumption was supported by the observation that introduction of further hydrophilic groups usually removes completely the fibrinolytic activity along with a rise of their salting-out effect[21]. In the series of 3- or 5-alkylsalicylic acids, Hansch and von Kaulla[22] analyzed the quantitative relationships between structure and activity and established the basic importance of lipophilicity for the activation of fibrinolysis. In the same group of acids von Kaulla and Ens[23] demonstrated that the substances diffuse into the coagulum where they induce the fibrinolysis by displacing the antiactivator from its binding to fibrin. We attempted to support von Kaulla's hypothesis of the mechanism of fibrinolysis activation using a series of prepared β-arylaliphatic acids. In this connection we examined the behaviour of acids *VI* in the presence of another blood protein, serum albumin. To evaluate the binding to serum albumin we used Mizushima's test[24] where the criterion of intensity of binding is the inhibition of heat denaturation of serum albumin.

To compare the effect we expressed these activities as functions of the physico-chemical properties of these acids. We made use of the method of correlating biological activity as developed by Hansch and coworkers[25–27], using substituent constants characterizing their contribution to the physico-chemical properties of the whole molecule. The equation expressing the biological activity as a function of electronic, hydrophobic and steric parameters of the substituents has the form

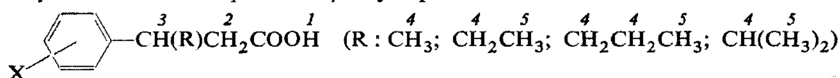
$$\log(1/C) = a\pi - b\pi^2 + c\sigma + dE_S + e\,, \qquad (3)$$

where C is the concentration which brings about the same biological effect, σ are polar constants, *e.g.* Hammett's or Taft's and E_S are steric parameters. Parameter π for substituent X is defined by[25,28]

$$\pi = \log P_X - \log P_H\,, \qquad (4)$$

TABLE I

Physico-Chemical Properties of β-Arylaliphatic Acids *VI*



Number	R X	M.p., °C (solvent)	pK^a	IR (KBr, cm^{-1})
VIa	CH_3 H	37–38[e] (n-hexane)	4·64 (4·65)	1 710
VIb	CH_3 4-CH_3O	66–67[f] (n-hexane)	4·73 (4·72)	1 715 840
VIc	CH_3 4-CH_3	92–93[g] (50% CH_3OH)	4·71 (4·70)	1 703 821
VId	CH_3 4-Cl	90–91[h] (50% CH_3OH)	4·60 (4·59)	1 710 831
VIe	CH_3 3-CF_3	84–86 (50% CH_3OH)	4·54 (4·54)	1 710 705
VIf	CH_3 4-Br	105–106 (50% CH_3OH)	4·57 (4·58)	1 710 825
VIg	CH_3 4-C_2H_5	67–68[i] (60% CH_3OH)	4·69 (4·69)	1 708 835[j]
VIh	CH_3 3-Br	37–39 (50% CH_3OH)	4·56 (4·55)	1 715 690
VIi	CH_3 4-iso-C_3H_7	76–78[k] (50% CH_3OH)	4·68 (4·69)	1 715 830
VIj	CH_3 4-C_6H_5	118–120[l] (80% CH_3OH)	4·64 (4·65)	1 710 828
VIk	CH_3 4-iso-C_4H_9	54–55 (60% CH_3OH)	4·66 (4·68)	1 710 847[j]
VIl	CH_3 4-HO	138–140[n] (50% CH_3OH)	4·77 (4·75)	1 705 830
VIm	C_2H_5 H	47–48[o] (50% CH_3OH)	4·68 (4·70)	1 690
VIn	C_2H_5 4-CH_3	58–59[p] (50% CH_3OH)	4·75 (4·74)	1 720 815
VIo	C_2H_5 4-Cl	67–68 (50% CH_3OH)	4·65 (4·62)	1 705 815
VIp	C_2H_5 4-iso-C_4H_9	53–54 (70% CH_3OH)	4·70 (4·72)	1 690 810

TABLE I
(*Continued*)

^{1}H-NMR ($CDCl_3$, p.p.m.)					$\sum\pi$	σ
1[b]	*2*[c]	*3*[d]	*4*	*5*		
11·35	2·57	3·20	1·28 d $J = 6{\cdot}0$	—	0·30	0
10·66	2·55	3·15	1·26 d $J = 6{\cdot}0$	—	0·31	—0·27
10·65	2·55	3·18	1·26 d $J = 6{\cdot}5$	—	0·75	—0·17
10·66	2·57	3·20	1·25 d $J = 6{\cdot}0$	—	1·00	0·23
10·74	2·55	3·25	1·28 d $J = 7{\cdot}0$	—	1·18	0·43
11·28	2·54	3·11	1·26 d $J = 6{\cdot}5$	—	1·20	0·27
11·10	2·55	3·19	1·27 d $J = 6{\cdot}0$	—	1·25	—0·15
11·10	2·55	3·18	1·27 d $J = 7{\cdot}0$	—	1·21	0·39
11·10	2·55	2·65— 3·50	1·25 d $J = 6{\cdot}0$	—	1·70	—0·15
11·35	2·55	3·21	1·26 d $J = 6{\cdot}0$	—	2·19	—0·01
11·04	2·56	3·20	1·27 d $J = 7{\cdot}0$	—	2·20	—0·11
11·10	2·55	3·18	1·27 d $J = 7{\cdot}0$	—	—0·31	—0·30
11·12	2·52	2·90	1·60 m	0·72 t $J = 6{\cdot}0$	0·80	0
10·80	2·55	2·85	1·60 m	0·76 t $J = 6{\cdot}0$	1·25	—0·17
9·84	2·54	2·70— 3·40	1·60 m	0·75 t $J = 6{\cdot}0$	1·50	0·23
11·60	2·55	2·85	1·1— 2·0 m	0·75 t $J = 6{\cdot}5$	2·70	—0·11

TABLE I
(*continued*)

Number	R X	M.p., °C (solvent)	pK^a	IR (KBr, cm^{-1})
VIr	iso-C_3H_7 H	46–47[r] (50% CH_3OH)	4·80 (4·80)	1 659
VIs	iso-C_3H_7 4-CH_3	74–76[t] (50% CH_3OH)	4·86 (4·84)	1 695 810
VIt	iso-C_3H_7 4-iso-C_4H_9	56–58 (70% CH_3OH)	4·84 (4·83)	1 705 800
VIu	n-C_3H_7 H	33–34[u] (60% CH_3OH)	4·77 (4·76)	1 705
VIv	n-C_3H_7 4-CH_3	89–90 (70% CH_3OH)	4·76 (4·81)	1 690 810
VIw	n-C_3H_7 4-Cl	68–69[w] (70% CH_3OH)	4·70 (4·70)	1 708 828

[a] Values in parentheses were computed from Eq. (*1*); [b] broad singlet; [c] doublet, $J = 7{\cdot}0$ Hz; [d] multiplet; literature references report m.p. (°C) of [e] 39–40 (ref.[6,9]); [f] 67–68 (ref.[7]); [g] 91–92 (ref.[10]); [h] 92–93 (ref.[11]); [i] 67–68 (ref.[12]); [j] measurement done in 5% $CHCl_3$; [k] 79–80 (ref.[13]);

where P_X and P_H are the partition coefficients in the system n-octanol–water for the substituted and unsubstituted compound, respectively, and it represents the contribution of the substituent to the overall lipophilic character of the molecule.

The experimental results of fibrinolysis activation by β-arylaliphatic acids are summarized in Table II. The table does not include β-(4-hydroxyphenyl)butyric acid (*VI l*) which is inactive in the measured concentration range and β-(4-isobutylphenyl)isovaleric acid (*VIt*) which is insoluble under the test conditions. Since acids *VI* are partly dissociated under the conditions of estimation of fibrinolytic activity, to express their efficiency we used expressions derived by Fujita[29] for the unionized (Eq. (*5*) and ionized (Eq. (*6*) forms:

$$\log(1/C_n) = \log(1/C) + \log\{([H^+] + K_a)/[H^+]\}\,, \quad (5)$$

$$\log(1/C_i) = \log(1/C) + \log\{([H^+] + K_a)/K_a\}\,, \quad (6)$$

where C_n is the concentration of unionized, C_i of ionized form, C is the total concentration, K_a is the dissociation constants of the corresponding acid and $[H^+]$ is the concentration of hydrogen ions in the extracellular phase. Relationships between the

TABLE III
(continued)

^{1}H-NMR ($CDCl_3$, p.p.m.)					$\sum\pi$	σ
1[b]	*2*[c]	*3*[d]	*4*	*5*		
10·98	2·30 – 3·00		1·80 m	0·88; 0·72[s] $J = 6{\cdot}0$	1·10	0
10·55	3·40 – 3·15		1·80 m	0·94; 0·76[s] $J = 6{\cdot}0$	1·55	−0·17
10·82	2·56	3·00	1·50 m	0·85 d $J = 6{\cdot}5$	3·00	−0·11
10·95	2·55	3·05	0·95– 1·80 m	0·82 t[v]	1·30	0
11·20	2·50	2·92	0·90– 1·80 m	0·80 t[v]	1·75	−0·17
11·10	2·52	2·96	0·80– 1·70 m	0·85 t[v]	2·00	0·23

[v] ref.[14] described the compound but does not report its m.p.; [n] 132–134 (ref.[15]); [o] 41 to [l]2·5 (ref.[6]); [p] 54–56 (ref.[16]); [r] 49–50 (ref.[17]); [s] two doublets; [t] 77 (ref.[18]); [u] 34–35 (ref.[19]); 4 deformed triplet; [w] 68–69 (ref.[19]).

fibrinolytic activity of β-arylaliphatic acids *VI* in the undissociated form and the physico-chemical quantities are described by equations (*7*)–(*10*) in Table III. In Eq. (*7*) we considered only the hydrophobic effect by summing the π parameters for substituents at the aromatic ring and of alkyls in the β position with respect to the carboxyl. In the later equations, the original Eq. (*7*) is extended to include the electronic effects of substituents X by introducing the polar constants σ (equation (*8*)) and the effect of β-alkyls which is characterized by an induction effect in Eq. (*9*) or by a steric effect in Eq. (*10*). The same approach was used for analyzing the fibrinolytic activity of acids *VI* in the ionized form and disregarding the dissociation, the resulting expressions being Eqs (*11*) and (*12*), analogous to Eq. (*10*). From a comparison of the coefficients at terms containing $\sum\pi$ in Eq. (*10*) and (*11*) it follows that the dependence of fibrinolytic activity of acids *VI* on their lipophilic character is not affected by dissociation. The differences in the coefficients with terms containing the E_S parameter are due to the dependence of dissociation constants implicit in the calculation of C_n and C_i, on these parameters. Hence Eq. (*12*) where the fibrinolytic activity is expressed by means of the total acid concentration, has practically the same statistical significance as Eqs (*10*) and (*11*). Application of other physico-chemical parameters, *i.e.* the

TABLE II

Biological Activity of β-Arylaliphatic Acids *VI* (concentrations C, C_n, C_i are expressed as molarity)

Compound	Fibrinolytic activity			Inhibition of denaturation SA		
	log (1/C)	log (1/C_n)	log (1/C_i)	log (1/C)	log (1/C_n)	log (1/C_i)
VIa	0·921	3·672	0·922	3·046	3·704	3·154
VIb	1·222	3·903	1·227	3·097	3·701	3·221
VIc	1·097	3·798	1·098	3·444	4·063	3·663
VId	1·222	4·032	1·225	3·495	4·200	3·590
VIe	1·301	4·162	1·302	3·577	4·323	3·663
VIf	1·347	4·197	1·347	3·602	4·315	3·695
VIg	1·347	4·078	1·348	3·770	4·396	3·886
VIh	1·347	4·197	1·347	3·569	4·306	3·656
VIi	1·699	4·430	1·700	3·863	4·490	3·980
VIj	2·097	4·848	2·098	4·022	4·680	4·130
VIk	2·097	4·818	2·098	4·125	4·759	4·239
VIm	1·046	3·747	1·047	3·310	3·929	3·429
VIn	1·222	3·883	1·223	3·495	4·084	3·624
VIo	1·523	4·304	1·524	3·561	4·242	3·662
VIp	2·301	4·982	2·302	4·086	4·690	4·210
VIr	1·222	3·823	1·230	3·252	3·797	3·397
VIs	1·398	3·959	1·399	3·475	3·992	3·632
VIu	1·222	3·863	1·229	3·611	4·185	3·745
VIv	1·523	4·114	1·524	3·688	4·227	3·837
VIw	1·824	4·525	1·825	3·830	4·449	3·949

Swain–Lupton constants R and F and of steric parameters of the substituents on the aromatic ring, just as the introduction of the square term $(\sum\pi)^2$ did not improve the correlation.

The regression equations permit one to conclude that the fibrinolytic activity of acids *VI* depends first of all on their lipophilicity and increases with the increasing lipophilic character of their substituents at the aromatic ring as well as of alkyls at the C_β atom. Eq. (*8*) shows this activity to be practically independent of the electronic effects of the aromatic substituents. In Eq. (*10*) the effect of β-alkyls is expressed by their steric hindrance characterized by the steric parameters E_S. Application of Taft's constants σ^* replacing the steric effect of the β-alkyls by their induction effect led to Eq. (*9*) with a similar statistical significance. The statistical resemblance of the two equations is due to the mutual correlation between E_S and σ^* of the β-alkyls as was discussed before. One thus cannot decide unequivocally about the character of the effect of the alkyls at the C_β atom on fibrinolytic activity. In both cases, however, this effect would be of auxiliary nature only. A comparison of acids differing only

in the alkyl in the β-position toward the carboxyl (*e.g. VIc*, *VIn*, *VIs*, *VIv* or *VId*, *VIo*, *VIw*) indicates that the negative steric or induction effect does not eliminate the positive effect of rising lipophilicity. Still there is no doubt that the rise of lipophilicity of β-arylaliphatic acids *VI* is achieved with advantage by substitution at the aromatic ring rather than by extending the chain in the β-position as follows from a comparison of acids with the same value of $\sum\pi$ but with a different β-alkyl. This holds for acids *VIf*, *VIg* and *VIn*, the $\sum\pi$ of which is 1·2 and 1·25, respectively, or for acids *VIi* and *VIv*, where the $\sum\pi$ is 1·7 and 1·75, respectively.

Together with the fibrinolytic activity we determined the binding of β-arylaliphatic acids *VI* to serum albumin by evaluating the inhibition of its heat denaturation. The experimental results shown in Table II were processed by regression analysis and the equations obtained are summarized in Table III. Comparison of analogous equations for fibrinolytic activity (*9*)–(*12*) and for inhibition of denaturation of serum albumin (*15*)–(*18*) points to the important similarity of the relationships between the two activities and the lipophilic character of acids *VI* as well as the steric, or induction effect of alkyls in the β-position with respect to the carboxyl. The similarity is exhibited by the similar values of the slopes for the individual physico-chemical parameters and demonstrates that the mechanism of action of β-arylaliphatic acids in the activation of fibrinolysis as well as in the inhibition of denaturation of serum albumin is of similar character.

The results of quantitative studies[27,30–33] of the relationship between the binding of compounds to proteins and their structure may be summarized in the following: *a*) The fundamental physicochemical property in a series of structurally related substances which affects their binding to a protein is their lipophilicity; *b*) the relationship between the binding to proteins and lipophilicity has generally the character of a linear dependence; *c*) the slope of this dependence lies within a relatively narrow range of 0·55 ± 0·10 for different structural types of compounds as well as for different types of proteins. Even these general observations support the assumption that the binding of β-arylaliphatic acids to one of the blood proteins plays an important role in the mechanism of fibrinolysis.

EXPERIMENTAL

Methods

The IR spectra of β-arylaliphatic acids *VI* were recorded in the region of 400–4000 cm^{-1} in a KBr pellet using a UR 20 (Zeiss, Jena) spectrophotometer. ^{1}H-NMR spectra were recorded in a ZKR 60 (Zeiss Jena) spectrometer using a 6% solution in deuteriochloroform, and tetramethylsilane as internal standard. The p*K* values of acids *VI* were determined conductometrically in water using an OK-102/1 (Radelkis, Hungary) conductometer, in a concentration range from 0·2 to 0·5 mM. The purity of the 1-aryl alkanols *II* and bromides *III* was checked by gas chromatography in a Fractometer (Perkin-Elmer F7) gas chromatograph. A stainless steel column with

TABLE III

Coefficients of Regression Equations of the General Type $Y = a + b \, . \, \Sigma\pi + c \, . \, \sigma + d \, . \, \sigma^* + e \, . \, E_S$

Equation number	Y	a	b	c	d	e	n	s	r	F
Fibrinolytic activity										
7	$\log(1/C_n)$	3·4164	0·5508	—	—	—	20	0·1817	0·8817	65·60
8	$\log(1/C_n)$	3·4109	0·5527	0·1993	—	—	20	0·1818	0·8925	33·28
9	$\log(1/C_n)$	3·4637	0·6030	—	2·1042	—	20	0·1182	0·9590	87·42
10	$\log(1/C_n)$	3·4515	0·5919	—	—	0·7835	20	0·1204	0·9543	86·68
11	$\log(1/C_i)$	0·6943	0·5905	—	—	0·4229	20	0·1200	0·9528	83·68
12	$\log(1/C)$	0·6921	0·5913	—	—	0·4228	20	0·1193	0·9534	84·86
Inhibition of serum albumin denaturation										
13	$\log(1/C_n)$	3·6383	0·4320	—	—	—	20	0·1617	0·8597	51·00
14	$\log(1/C_n)$	3·6308	0·4347	0·2725	—	—	20	0·1551	0·8792	28·92
15	$\log(1/C_n)$	3·6859	0·4844	—	2·1131	—	20	0·0745	0·9735	153·92
16	$\log(1/C_n)$	3·6702	0·4688	—	—	0·7118	20	0·1038	0·9478	75·15
17	$\log(1/C_i)$	3·1157	0·4695	—	—	0·3647	20	0·0915	0·9564	91·14
18	$\log(1/C)$	3·0079	0·4697	—	—	0·4504	20	0·0913	0·9569	92·28

TABLE IV

Characterization of Intermediates *II*, *III*, *IV*

Series	B.p., °C/Torr		For *IV* calculated/found	
	II / *III*	*IV*	% C	% H
a	105–106/20	128–130/1	68·16	7·63
	92– 94/16		68·39	7·59
c	112–113/14	104–111/17	69·04	7·97
	104–111/17		68·87	7·87
d	129–131/18	139–140/0·8	60·30	6·41
	119–122/14		60·39	6·57
e	94– 95/10	142–143/1·2	57·83	5·76
	90– 91/11		57·95	5·82
f	128–129/10	139–140/0·3	52·49	5·58
	124–125/10		52·62	5·76
g	122–123/16	160–161/1·5	69·84	8·27
	114–118/11		70·04	8·19
h	130–131/10	135–136/0·1	52·49	5·58
	123–124/10		52·62	5·42
i	120–121/10	151–153/0·5	70·56	8·55
	122–124/10		70·79	8·73
j	72– 74[a]	—	—	—
	87– 89[a]			
k	140–141/16	—	—	—
	130–132/14			
m	100–101/11	113–114/0·5	69·04	7·97
	96– 97/12		70·28	8·07
n	106–107/9	129–130/0·7	69·84	8·27
	104–105/9		70·01	8·41
l	117–118/9	134–135/0·6	61·44	6·77
	114–115/10		61·62	6·83
p	129–130/9	162–164/2	71·82	9·04
	130–131/9		71·82	9·17
r	103–104/10	132–133/1	69·84	8·28
	104–105/10		70·05	8·39
s	107–108/9	125–126/0·6	70·56	8·55
	110–111/9		70·73	9·46
t	134–135/9	—	—	—
	137–138/9			
u	119–120/15	141–142/1·8	69·84	8·27
	110–112/11		69·97	8·49
v	115–116/9	148–150/2	70·56	8·55
	111–112/9		70·69	8·73
w	131–132/10	155–156/2	62·47	7·09
	129–130/10		62·67	7·21

[a] M.p. (°C).

a 3 mm diameter and 2 m length was filled with Gas-Chrom Q 125-150 μm, wetted with 3% polyethylene glycol (mol. wt. about 20000). The melting points were determined in a Boëtius M block and are not corrected.

For substituents at the benzene ring, parameters π derived for arylacetic acids were used[28,34], for alkyls at the C_β atom they were computed from the increments $\Delta\pi = 0.5$ for CH_2 and $\Delta\pi = -0.2$ for branching[35]. The Hammett constants σ of aromatic substituents were taken over from ref.[36], the Taft constants σ^* and steric parameters E_S of the β-alkyls from ref.[37]. The coefficients of the regression equations were calculated from experimental data by a multiple regression analyses. The statistical significance of the individual parameters was evaluated by the F-test at a 99% level of significance, changing the parameters one by one. In multiparameter equations there is the risk of occurrence of accidental correlations unless the number of experimental data as compared with the number of parameters is large enough. An analysis carried out before[38] showed that if each variable is composed of at least five experimental values, the possibility of occurrence of accidental correlations is very small indeed. This prerequisite was met for all the equations shown here.

The activation of fibrinolysis was investigated by the "hanging clot" method[20] prepared from human plasma and suspended in the solution of the tested compound. The compounds were dissolved in Tris-buffer (pH 7·42) with an addition of 5%(v/v) acetone. The efficiency was expressed by the minimum molarity which dissolved the coagulum completely after 24 h of incubation at 37°C.

Inhibition of heat denaturation of bovine serum albumin was estimated according to Mizushima[24]. Serum albumin was dissolved in phosphate buffer (pH 5·3) and, using four concentrations of the compound tested, the percentage inhibition of denaturation was measured in comparison with a control solution of serum albumin. Graphic interpolation was used for determining the efficiency as concentration in mol l^{-1}, bringing about 50% inhibition.

1-(Aryl)alkanols (*II*)

A solution of sodium borohydride prepared, from 15 g hydride and 300 ml water stabilized with 0·2 ml sodium hydroxide was added dropwise under stirring at −3°C to a solution of 0·3 mol of the appropriate alkylaryl ketone in 75 ml methanol and the mixture was stirred for 5 h at 20°C. After distilling off the methanol, the residue was diluted with 150 ml water and, under cooling to 15°C, the solution was acidified with hydrochloric acid (1 : 1) to pH 5. The separated oil was extracted with three times 100 ml ether and the combined ether extracts were washed with water and dried with magnesium sulfate. After distilling off the solvent, the products were isolated by distillation *in vacuo* in a yield of 70—85%. The boiling points are shown in Table IV.

1-(Aryl)alkyl Bromides (*III*)

Phosphorus tribromide (12·5 g) was added dropwise to a mixture of 0·1 mol 1-(aryl)alkanol *II* and 0·7 ml pyridine in 20 ml ether at −5°C. The mixture was stirred for 2·5 h at 20°C and poured onto 100 g mixture of ice and water. After separation of the organic phase, the organic layer was extracted twice with 100 ml ether. The extracts combined with the main portion were washed twice with 50 ml 5% $NaHCO_3$, twice with 100 ml water and dried with magnesium sulfate. After concentration, the crude products were distilled *in vacuo* in a 70—80% yield. With *IIId*, *IIIf*, *IIIg*, *IIIi*, *IIIn*, *IIIp*, *IIIt*, the bromine content was assayed. The boiling points of the products are shown in Table IV.

Ethyl 1-(Aryl)alkylmalonates (*IV*)

Ethyl malonate (16 g) was added to a solution of 2·3 g sodium in 50 ml ethanol and, under stirring at 20°C, this was followed over a period of 20 min by a dropwise addition of 0·1 mol bromide *III*. The mixture was boiled for 8 h. After cooling, the ethanol was removed by distillation, the residue was diluted with 100 ml water and the product was extracted with three times 100 ml ether. The ether extracts were washed twice 100 ml water and dried with magnesium sulfate. The ether was distilled off and the products were isolated by vacuum distillation in 60—75% yields. The boiling points and elementary analyses are shown in Table IV. Compounds *IVj*, *IVk* and *IVt* were used in the crude state.

1-(Aryl)alkylmalonic Acids (*V*)

A mixture of 0·27 mol malonate *IV*, 35 ml ethanol, 15 ml water and 25 ml 5M-KOH was boiled for 2 h. After cooling, the ethanol was distilled off and the residue was diluted with 70 ml water. The solution was filtered with charcoal and the filtrate was acidified with hydrochloric acid to pH 4 at 5—10°C. The crude products obtained were washed with water, dried at 50°C and processed further. Compounds *Vj*, *Vk* and *Vt* were identified by elementary analysis after crystallization from ethanol. *Vj*: for $C_{17}H_{16}O_4$ (284·3) calculated: 71·81% C, 5·67% H; found: 72·29% C, 5·78% H; *Vk*: for $C_{15}H_{20}O_4$ (264·3) calculated: 68·16% C, 7·63% H; found: 68·35% C, 7·68% H; *Vt*: for $C_{17}H_{24}O_4$ (292·4) calculated: 69·84% C, 8·27% H; found: 69·99% C, 8·33% H.

β-Arylaliphatic Acids (*VI*)

0·5 mol acid *V* was heated for 20 min to 180—200°C. After cooling to 50°C, the oil was dissolved in 50 ml 1M-NaOH. After dilution with 50 ml water the solution was filtered with charcoal and acidified with hydrochloric acid to pH 2. After cooling to 5°C, the precipitated solid was filtered, washed with water to a neutral reaction and crystallized from a suitable solvent. The physico-chemical parameters are shown in Table I. *VIe*: for $C_{11}H_{11}F_3O_2$ (232·2) calculated: 56·90% C, 4·77% H, 24·55% F, found: 56·96% C, 4·79% H, 24·45% F; *VIf*: for $C_{10}H_{11}BrO_2$ (243·1) calculated: 49·40% C, 4·56% H, 32·88% Br; found: 49·15% C, 4·55% H, 33·05% Br; *VIh*: for C_{10} . . $H_{11}BrO_2$ (243·1) calculated: 49·40% C, 4·56% H, 32·88% Br, found: 49·25% C, 4·54% H, 33·11% Br; *VIk*: for $C_{14}H_{20}O_3$ (220·3) calculated: 76·33% C; 9·15% H; found: 76·50% C, 9·35% H; *VIo*: for $C_{11}H_{13}ClO_2$ (212·7) calculated: 62·12% C; 6·16% H, 16·67% Cl, found: 61·98% C, 6·32% H, 16·80% Cl; *VIp*: for $C_{15}H_{22}O_2$ (234·3) calculated: 76·89% C, 9·46% H; found: 76·81% C, 9·73% H; *VIt*: for $C_{16}H_{24}O_2$ (248·3) calculated: 77·37% C, 9·74% H; found: 77·45% C, 9·89% H; *VIv*: for $C_{13}H_{18}O_2$ (206·3) calculated: 75·69% C, 8·80% H; found: 75·66% C, 9·01% H.

The elementary analyses were done at the department of microanalysis of the Research Institute of Pharmacy and Biochemistry (director Dr J. Körbl). The IR spectra were measured by Mrs P. Vejdělková, the pK values were determined by Dr Z. Bacík, under the direction of Dr B. Kakáč; gas chromatographic analyses were done by Mr S. Vaněček.

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